genetically engineered to produce therapeutic compounds, and pre-differentiated prior to administration into the CNS.

Original claims 1-20, are pending in the application.

Applicants are pleased to acknowledge that the Examiner has withdrawn her previous rejections of the claims under 35 U.S.C. §112, second paragraph, as being indefinite.

Rejection of Claims 1-18, Under 35 U.S.C. § 112, first paragraph

Claims 1-18 stand rejected under 35 U.S.C. § 112, first paragraph, because in the Examiner's opinion, cell and gene therapy using marrow stromal cells are not enabled by the disclosure in the specification given the unpredictability of the art at the time of filing. The Examiner cites the following references in support of her rejection: Prockop (1997, Science 276:71-74), Gerson (1999, Nature Med. 5:262-264), Sanberg and Willing (1998, Nuc. Acids Symp. Ser. 38:139-142) (hereinafter referred to as "Sanberg"), and Sabaté et al. (1996, Clin. Neurosci. 3:317-321) (hereinafter referred to as "Sabaté").

Applicants respectfully submit that the claimed cell and gene therapy methods are enabled by the specification as filed under the current law pursuant to 35 U.S.C. § 112, first paragraph. Applicants incorporate by reference the arguments set forth in the Amendment filed on February 10, 2000, as if set forth herein in their entirety.

It is well-settled that an Applicant need not have actually reduced the invention to practice prior to filing. MPEP §2164.02 (citing *Gould v. Quigg*, 822 F.2d 1074 (Fed. Cir. 1987)). Indeed, the invention need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation. *In re Borkowski*, 422 F.2d 904, 908 (C.C.P.A. 1970). The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. MPEP §2164.01 (citing *In re Angstadt*, 537 F.2d 498, 504 (C.C.P.A. 1976)). The fact that

experimentation may be complex does not necessarily make it undue if the art typically engages in such experimentation. *Id.* Further, the specification need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known to those skilled and already available to the public. MPEP §2164.05(a) (citing *In re Buchner*, 929 F.2d 660, 661 (Fed. Cir. 1991)). Therefore, under current law, enablement does not require a working example and experimentation is allowed so long as it is not undue.

Initially, Applicants respectfully point out that Prockop, which is not a "prior art" reference, is not a post-filing date reference for purposes of 35 U.S.C. § 112, first paragraph. This is because this application, which is a continuation-in-part of PCT Application No. US/PCT96/04407, was filed on February 24, 1998, and Prockop was apparently published in April of 1997, which is less than one year prior to the filing of the instant application. It is settled that under 35 U.S.C. §102, a printed publication by an applicant disclosing his or her own work published within one year prior to filing an application for patent therefor cannot be prior art for purposes of 35 U.S.C. §102(a) since the invention was not known or used "by others" or patented or described before his or her own invention thereof as required by the statute.

Therefore, since Prockop, on which the co-inventor of the present invention, Darwin J. Prockop, is sole author, was published less than one year before the filing date of this application, *i.e.*, February 24, 1998, the reference cannot be prior art with respect to the subject matter disclosed in the reference, if any, which is claimed in the instant application.

Even though Prockop is not "prior art" with regard to the instant invention, Prockop is not a "post-filing date" reference since it was published in April of 1997, which was before the filing date of the instant application. Thus, regardless of the holding of *In re Wright*, 27 USPQ2d 1510 (Fed. Cir. 1993), Prockop is not a post-filing date reference and cannot be used by the Examiner to show "that a particular invention is not possible years after the filing date." Office Action at page 5 (quoting

In re Wright, 27 USPQ2d at 1513-14)(emphasis added). Therefore, Prockop does not support the rejection under 35 U.S.C. §112, first paragraph, for lack of enablement.

Applicants previously provided extensive discussion as to why Gerson, Sanberg, and Sabaté do not support a rejection under 35 U.S.C. §112, first paragraph, for lack of enablement, in the Amendment filed February 10, 2000, and those arguments are incorporated by reference herein as if set forth in their entirety.

The Examiner now argues, at pages 5-6 of the Office Action, that the specification does not teach how to treat a CNS disease and that Horwitz et al. (1999, Nature Med. 5:309-313), a copy of which is enclosed herewith and on which co-inventor Darwin J. Prockop is a co-author, does not support enablement since it relates to treatment of osteogenesis imperfecta (OI), which is not a CNS disease. Similarly, at pages 7-8, the Examiner argues that successful transfection of isolated stem cells using constructs encoding collagen do not provide guidance with respect to treatment of CNS disease.

Further, the Examiner, at page 8 of the Office Action, contends that post-filing reduction to practice as demonstrated in Schwartz et al. (1999, Human Gene Therapy 10:2539-2549), a copy of which is enclosed herewith and on which co-inventors Darwin J. Prockop and Ausim Azizi are co-authors, does not support enablement of the present invention. That is, although the Examiner apparently acknowledges that Schwartz et al., demonstrates the successful treatment of a CNS disease according to the teachings of the present invention, the Examiner insists that enablement under 35 U.S.C. §112, first paragraph, somehow requires "more."

Particularly, Schwartz et al., demonstrates the successful treatment of a CNS disease, *i.e.*, Parkinson's Disease, according to the teachings provided in the specification as filed in that human MSCs were transduced using retroviral vectors and expressed two therapeutic proteins, *i.e.*, tyrosine hydroxylase and/or GTP cyclohydrolase I. The genetically engineered cells synthesized L-DOPA (3,4-dihydroxyphenylalanine) and, when injected into the striatum of 6-hydroxydopamine-lesioned rats, which is an art-recognized rat model of Parkinson's disease, the cells

became engrafted, produced L-DOPA, and provided a significant reduction in the lesioned phenotype, *i.e.*, engraftment by genetically engineered MSCs reduced apomorphine-induced contralateral rotation in 6-hydroxydopamine-lesioned rats (Schwartz et al., at page 2543, Figure 2).

In the face of this additional reduction to practice demonstrating the successful treatment of a CNS disease using genetically engineered MSCs according to the teachings of the present invention, the Examiner argues that "one demonstration of the use of MSCs encoding a particular protein associated with a particular disease model is not representative of the level of skill in the art, nor is it predictive of successful use of MSCs transfected or transduced with any and all proteins to treat any and all central nervous system diseases or disorders." Office Action at page 8. Therefore, where not even one working example is required for enablement under 35 U.S.C. §112, first paragraph, the Examiner is apparently demanding that treatment of each and every CNS disease must first be reduced to practice before the claimed methods can be patented. Applicants respectfully submit that this is simply not the law under the patent statute.

The law is well-settled that extensive experimentation is not undue if one of ordinary skill in the art routinely engages in such experimentation. Further, Horwitz et al. and Schwartz et al. demonstrate the high degree of skill in the art, the extensiveness of experimentation routinely performed by the artisan, and that one skilled in the art of gene and cell therapy typically engaged in this type of experimentation at the time the application was filed. This is important, since the present case law regarding enablement under 35 U.S.C. §112, first paragraph, allows significant experimentation without finding it undue if the art typically engages in such experimentation.

Moreover, under the present law of enablement, generic claims reciting large numbers of species are allowable without disclosure of every species so long as the art engages in experimentation to identify the operative species encompassed by the generic claim. In *In re Vaeck*, 20 USPQ2d 1438, 1445 (Fed. Cir. 1991), reviewing an

enablement rejection of a broad claim reciting methods for producing insect proteins in cyanobacteria, the Court of Appeals for the Federal Circuit discussed enablement in the context of generic species claims:

> we do not imply that patent applicants in art areas currently denominated as "unpredictable" must never be allowed generic claims encompassing more than the particular species disclosed in their specification. It is well settled that patent applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art. *In re Angstadt*, 537 F.2d 498, 502-03, 190 USPQ 214, 218 (CCPA 1976). However, there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and how to use the invention as broadly as it is claimed. This means that the disclosure must adequately guide the art worker to determine, without undue experimentation, which species among all those encompassed by the claimed genus possess the disclosed utility.

In re Vaeck, 20 USPQ2d at 1445 (emphasis added). Thus, not every species need be disclosed where one skilled in the art would be able, without undue experimentation, to determine which species possess the disclosed utility. *See also In re Druey*, 145 USPQ 219, 221 (Bd. Pat. App. & Int. 1965)("The fact that not all possible substituents encompassed by the generic language are illustrated does not preclude appellants from asserting the genus when no reasons have been advanced by the examiner to rebut appellants' assertion that all the compounds embraced by the genus will in fact have the properties ascribed to them."). Thus, each particular CNS disease and each particular protein associated with the disease need not be reduced to practice before the present methods are enabled.

The MPEP at § 2164.08(b), discussing inoperative subject matter, states:

> The presence of inoperative embodiments within the scope of a claim does not necessarily render a claim non-enabled. The standard is whether a skilled person could

> determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art. *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 224 USPQ 409, 414 (Fed. Cir. 1984) (prophetic examples do not make the disclosure nonenabling. . . . A disclosure of a large number of operable embodiments and the identification of a single inoperative embodiment did not render a claim broader that the enabled scope because undue experimentation was not involved in determining those embodiments that were operable. *In re Angstadt*, 190 USPQ 214, 218 (CCPA 1976).

Thus, inoperative embodiments do not necessarily render a claim nonenabled as long as the experimentation required to identify the operative species is not undue.

In the landmark enablement case of in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988), the court discussed the adequacy of disclosure with regard to a patent disclosing an immunoassay method for the detection of hepatitis B antigen using monoclonal antibodies. The *Wands* Court noted that of 143 hybridomas produced, only nine were assayed and, of those, only four hybridomas secreted IgM antibodies and exhibited a binding affinity constant for the HBsAg determinants of at least 10^9 M^{-1}, a "respectable 44 percent rate of success." *In re Wands*, 8 USPQ2d at 1406. Finding the claims were enabled, the *Wands* Court stated:

> Wands' disclosure provides considerable direction and guidance on how to practice their invention and presents working examples. There was a high level of skill in the art at the time when the application was filed, and all of the methods needed to practice the invention were well known .
>
> The nature of monoclonal antibody technology is that it involves screening hybridomas to determine which ones secrete antibody with desired characteristics. Practitioners of this art are prepared to screen negative hybridomas in order to find one that makes the desired antibody. No evidence was presented by either party on

> how many hybridomas would be viewed by those in the art as requiring undue experimentation to screen.

In re Wands, 8 USPQ2d at 1406 (emphasis added). Therefore, where, as here, the art typically screens administering of gene and cell therapies for various CNS diseases, wherein the protein product associated with the disease is known, in order to identify effective CNS therapies, one skilled in the art would not require undue experimentation to practice the invention commensurate with the scope of claims 1-18 without undue experimentation. Thus, where one skilled in the art routinely screens potential CNS therapies comprising administering MSCs as disclosed in the specification as filed to find a CNS therapy for a CNS disease of interest, having to do so is not the undue experimentation proscribed by 35 U.S.C. § 112, first paragraph, under the reasoning of *In re Wands*.

In *In re Angstadt*, 190 USPQ 214 (CCPA 1976), the court addressed the level of experimentation in an unpredictable art, *i.e.*, the chemical arts, where the claimed invention involved a method of catalytically producing hydroperoxides where the specification admitted that not all disclosed complexes produced the hydroperoxides. The *Angstadt* Court, holding that the invention as claimed was enabled, reasoned:

> We note that many chemical processes, and catalytic processes particularly, are unpredictable. . . .
>
> Appellants have apparently not disclosed every catalyst which will work; they have apparently not disclosed every catalyst which will not work. The question, then, is whether in an unpredictable art, section 112 requires disclosure of a test with every species covered by a claim. To require such a complete disclosure would apparently necessitate a patent application or applications with "thousands" of examples or the disclosure of "thousands" of catalysts along with information as to whether each exhibits catalytic behavior resulting in the production of hydroperoxides. More importantly, such a requirement would force an inventor seeking adequate patent protection to carry out a prohibitive number of actual experiments. This would tend to discourage

> inventors from filing patent applications in an unpredictable area since the patent claims would have to be limited to those embodiments which are expressly disclosed. A potential infringer could readily avoid "literal" infringement of such claims by merely finding another analogous catalyst complex which could be used in "forming hydroperoxides."

In re Angstadt, 190 USPQ at 218 (emphasis added) (citations omitted). Similarly, in *In re Bundy*, 209 USPQ 48, 52 (CCPA 1981), the court noted the public policy reasons mitigating against imposing a requirement that each compound be tested before a generic species claim would is allowed:

> Early filing of an application with its disclosure of novel compounds which possess significant therapeutic use is to be encouraged. Requiring specific testing of the thousands of prostaglandin analogs encompassed by the present claim in order to satisfy the how-to-use requirement of § 112 would delay disclosure and frustrate, rather than further, the interests of the public.

Thus, where methods for assessing the effectiveness of a CNS therapy are well-known in the art and/or are disclosed in the specification and where the method of treating a CNS disease by administering MSCs is extensively disclosed and reduced to practice in the specification as filed and has been further reduced to practice by following the teachings of the invention (*see*, *e.g.*, Horwitz et al., and Schwartz et al.), it would not be undue experimentation to screen for effective CNS therapies using the methods of the present invention where the art typically engages in such experimentation.

More recently, in *Ex parte Mark*, 12 USPQ2d 1904 (Bd. Pat. App. & Int. 1989), the Board reversed the Examiner's rejection for lack of enablement under 35 U.S.C. § 112, first paragraph, with regard to an application involving admittedly "innumerable" muteins (*i.e.*, mutated protein variants of the naturally-occurring protein) comprising a non-essential cysteine which exhibit biological activity after modification to substitute the cysteine. In reversing the Examiner, the *Mark* Court

stated:

> To the extent that the examiner is concerned that undue experimentation would be required to determine other proteins suitable for use in the present invention, we find [an applicant]'s declaration to be persuasive that only routine experimentation would be needed for one skilled in the art to practice the claimed invention for a given protein. The fact that a given protein may not be amenable for use in the present invention in that the cysteine residues are needed for the biological activity of the protein does not militate against a conclusion of enablement. One skilled in the art is clearly enabled to perform such work as needed to determine whether the cysteine residues of a given protein are needed for retention of biological activity.

Ex parte Mark, 12 USPQ2d at 1907. Therefore, where one skilled in the art routinely assays the compounds for the asserted utility, it is not undue experimentation for them to do so. Similarly, where the invention discloses methods of treating CNS disease comprising administering MSCs, not every disease or therapeutic protein associated with each disease must be successfully treated according to the methods of the invention before such methods can be patented.

The specification as filed, and the additional post-filing reduction to practice, amply support that the claimed methods are enabled under 35 U.S.C. §112, first paragraph. For instance, the extensive disclosure concerning how the presence of MSCs effects treatment further supports that one skilled in the art, armed with the teachings of the instant invention and the knowledge of the prior art, would be able to determine without undue experimentation what diseases, disorders or conditions of the CNS are suitable for treatment by administering isolated stromal cells. That is, knowing how the present invention works makes clearer to the skilled artisan which diseases, disorders, or conditions will respond to the treatment methods disclosed by Applicants in the present application. Thus, for a CNS disease, disorder, or condition for which the disease mechanism is understood, one skilled in the art, based upon the disclosure provided in the specification, would be able to determine whether the

disease is amenable to such treatment and treat the disease as disclosed in the specification as filed without undue experimentation.

The specification as filed makes clear, commencing at page 9, that isolated stromal cells can be used to replace CNS cells lost as a result of genetic disease, trauma, or other injury. The types of diseases, disorders, or conditions which are treatable using MSCs introduced directly into the CNS are set forth starting at page 16, line 8. They include genetic diseases of the CNS (*e.g.* Tay-Sachs disease, Krabbe's disease, Sandhoff's disease, and the like), birth-associated trauma, adult diseases of the CNS (*e.g.*, Parkinson's, Huntington's, Alzheimer's, ALS, epilepsy, and such), spinal cord injuries, and CNS tumors. Based upon the disclosure provided in the specification, one skilled in the art would appreciate which diseases, disorders or conditions can be effectively treated using MSCs and how these can be identified and treated according to the methods disclosed in the specification as filed and reduced to practice by Applicants without undue experimentation.

Further, the specification at pages 15-22 teaches the mechanism by which MSCs effect treatment (*e.g.*, by replacing cells lost due to a disease, disorder, or condition, by producing a molecule either not produced, not produced in sufficient amounts, or not produced in functional form, by mediating arrest of tumor growth and/or apoptosis, and the like). Based upon this extensive disclosure of how MSCs effect their therapeutic effects, one skilled in the art would not have to engage in undue experimentation to identify which genetic diseases, tumors or traumas can be effectively treated using MSCs.

As stated previously elsewhere herein, based upon the disclosure provided in the specification, one skilled in the art would not have to engage in any undue experimentation to determine which disease, disorder or condition can be treated using direct transplantation of isolated stem cells. Indeed, a large number of CNS diseases, disorders or conditions that can be treated using MSCs is set forth in the specification as filed such that the disease, disorder or condition includes, but is not limited to, stroke, trauma, brain tumor, Alzheimer's, Parkinson's, Huntington's,

Krabbe's, Tay-Sachs, and Sandhoff's diseases, Hurler's syndrome, epilepsy, birth trauma, spinal cord injury, and amyotropic lateral sclerosis.

Given that the skilled artisan would not have to engage in undue experimentation to determine which CNS disease, disorder or condition can be effectively treated using MSCs, and how to effect such treatment, based upon the teachings of the present invention, the claims are enabled. Indeed, Schwarz et al., *supra*, following the teachings of the present specification, transduced isolated MSCs with a vector comprising one or more therapeutic proteins, which when expressed, mediate the production of L-DOPA in the isolated stem cells. The MSCs, which were co-transduced with both nucleic acids, produced L-DOPA both *in vitro* and *in vivo*. Indeed, engraftment of the transduced MSCs expressing the therapeutic proteins mediated a detectable improvement in the condition of rats in an art-recognized model of Parkinson's disease.

Further, no undue experimentation would be required for the skilled artisan, based upon the disclosure provided in the specification, to determine which nucleic acid is required in the introduction step. As stated previously elsewhere herein, nucleic acids encoding therapeutic proteins useful for treating a CNS disease, disorder or condition are well known in the art. *See*, *e.g.*, Sabaté et al., *supra* (cited by the Examiner for other reasons). Further, the specification sets forth a variety of genetic and other diseases, disorders and conditions that can be treated by inserting an isolated nucleic acid into isolated stromal cells and then transplanting the transfected stromal cells into a human patient. *See*, *e.g.*, specification at pages 37-53. Moreover, the present invention has been further reduced to practice by Schwarz et al., *supra*, wherein following the teachings of the instant application, two nucleic acids encoding two therapeutic proteins (*i.e.*, tyrosine hydroxylase and GTP cyclohydrolase I) have been introduced into isolated stromal cells using a retrovirus vector and the transduced stromal cells have been used to effectively treat rats in an art-recognized rat model of Parkinson's disease.

In addition, the specification at pages 40-42, discloses various well-known methods for introducing an isolated nucleic acid into an isolated stromal cell (*e.g.*, electroporation, retrovirus infection, lipofectamine transfection, calcium phosphate, DEAE dextran, nuclear injection, and the like) as well as assays to determine the successful expression as well as the level of expression of the therapeutic protein encoded thereby (specification at pages 42-56). *See also* Schwarz et al., *supra.*

In sum, the disclosure in the specification as filed amply supports methods of treating a human patient having a disease, disorder or condition of the CNS comprising administering isolated stromal cells to the CNS of the patient and further supports such methods comprising cells comprising an isolated nucleic acid encoding a therapeutic protein. The specification supports such methods because even though no working example is required under current law, there has been extensive reduction to practice in this instance. Further, the instant application only omits that which is well-known to those skilled in the art and that which is already known to the public.

Applicants successfully transplanted both human and rat MSCs into the brains of rats (specification at pages 49-53). The data disclosed in the specification demonstrate that the donor cells were readily engrafted into the brain of recipient animals where the cells migrated into multiple areas including, but not limited to, the contralateral cortex, temporal lobe regions, cerebral cortex, rostrocaudal axis in the striatum, and the corpus callosum, where they remained localized. Thus, Applicants have demonstrated, for the first time, that rat and human MSCs can engraft, migrate, and survive in the brains of recipient animals.

Additionally, following the teachings of the specification as filed, Applicants have further reduced their invention to practice. That is, Schwarz et al. is representative of the level of skill in the art and demonstrates that the skilled artisan, armed with the teachings of the instant invention, would be able to practice the invention commensurate with the scope of the claims without undue experimentation.

Following the teachings of the instant invention as disclosed in the specification, a person of ordinary skill in the art would be able to engraft MSCs

producing a therapeutic protein into the CNS of a human recipient thereby treating a disease, disorder or condition of the CNS in the recipient without undue experimentation. The specification discloses that MSCs can engraft various tissues in a recipient including the brain where they express a therapeutic protein. Based on these teachings and methods well-known in the art, one of ordinary skill would be able to practice the claimed invention and nothing more is required under 35 U.S.C. §112, first paragraph.

Further, based upon the disclosure provided in the specification and methods well-known in the art, one of ordinary skill would be able to introduce an isolated nucleic acid encoding a therapeutic protein into MSCs and then engraft the CNS of a human recipient using the recombinant MSCs thereby treating a disease, disorder, or condition of the CNS mediated by the therapeutic protein without undue experimentation. Therefore, claims 1-18 are enabled under 35 U.S.C. §112, first paragraph, and the rejection of these claims for lack of enablement should be reconsidered and withdrawn.

Rejection of Claims 19 and 20, Under 35 U.S.C. § 103(a)

Claims 19 and 20 stand rejected under 35 U.S.C. § 103(a) as apparently being, in the Examiner's view, unpatentable Pereira et al. (1995, Proc. Natl. Acad. Sci. USA 92:4857-4861) ("Pereira"), taken with Friedmann (1994, TIG 10:210-214) ("Friedmann"), and Caplan (1991, J. Orthopaedic Research 9:641-650) ("Caplan"). The Examiner contends that Pereira discloses *in vivo* repopulation of tissue, including brain, by adherent marrow cells suggestive that the cells are long-term precursor cells for these tissues. The Examiner further contends that Caplan teaches that the progression from stem cell to final end phenotype *in vivo* depends on a myriad of factors, including "positional information" and local cueing from surrounding cells as well as signals emitted by the cell itself. Further, the Examiner contends that Friedmann discloses *in vivo* data demonstrating that mammalian CNS contains some cellular elements that are probably derived from bone marrow.

The Examiner then reasons, based on the combined teachings of Pereira, Friedmann and Caplan, that the combination of these references renders methods of directing MSC differentiation *in vivo* by co-culturing the cells with differentiated cells, *e.g.*, to produce astrocytes, obvious. Applicants respectfully submit that the combination of Pereira, Friedmann, and Caplan does not render claims 19 and 20 *prima facie* obvious under 35 U.S.C. §103(a), for the following reasons.

Preliminarily, the three-prong test which must be met for a reference or a combination of references to establish a *prima facie* case of obviousness has not been satisfied in the instant matter. The MPEP states, in relevant part:

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all of the claim limitations. MPEP § 2142.

None of these criteria have been met here.

Pereira, combined with Friedmann and Caplan, does not teach or suggest all of the claim limitations. More specifically, claims 19 and 20 recite that the method of directing the differentiation of an isolated marrow stromal cell comprises culturing the cell in the presence of a population of differentiated cells whereby the stromal cell differentiates into a cell of the same type as the cells it is co-cultured with. The combination of references urged by the Examiner does not teach these claim limitations. Indeed Pereira, Friedmann and Caplan do not mention any methods of *in vitro* culturing isolated stromal cells at all much less methods of co-culturing the cells with other cells in order to direct differentiation of the MSCs along a desired path. Pereira discloses only the administration of bone marrow-derived cells from a donor and tracing their subsequent fate in a recipient animal (*e.g.* where do the cells localize and what, if any, cell lineage-specific markers do they express). Therefore, Pereira

merely discloses a passive observation and nowhere does Pereira teach or suggest that the differentiation process can be directed. Therefore, Pereira has nothing whatsoever to do with culturing isolated stromal cells or directing their differentiation in any way.

Similarly, Friedmann's discussion of stromal cells is limited to two paragraphs at page 212. In these paragraphs, Friedmann does not mention directing the differentiation of stromal cells at all but only discusses that since the mammalian CNS contains cells probably derived from bone marrow, bone marrow may be a useful source of cells which can be genetically engineered and introduced into the CNS to deliver a therapeutic gene product. There is no discussion in Friedmann concerning differentiation of stromal cells at all much less how this might be directed *in vitro*.

Caplan does not correct the deficiencies of Pereira and Friedmann since Caplan does not teach or suggest that MSCs can be directed to differentiate either *in vivo* or *in vitro*. Caplan states, at page 641: "Although difficult to reconstruct on a cell culture dish, such 'positional information' has been experimentally approached by studying embryonic cells in culture." Indeed, Caplan teaches that differentiation from stem cell to final end phenotype is a *in vivo* complex process comprising a plethora of factors including paracrine and autocrine regulation. Thus, Caplan is, at the very most, merely an invitation to experiment to identify the various factors involved in stem cell differentiation, but there is nothing in Caplan which suggests that such trial-and-error transfection would be successful. Moreover, it is well-settled that an invitation to experiment is insufficient to support an obviousness rejection under 35 U.S.C. §103(a).

Further, there would have been no motivation to combine Pereira, Friedmann and Caplan to produce a method of directing stromal cell differentiation *in vitro* by co-culturing the stromal cell with differentiated cells. This is because Pereira, Friedmann and Caplan, alone or combined with the other references, does not teach or suggest directed differentiation of an isolated stromal cell and certainly does not teach or suggest how to direct differentiation *in vitro* by co-culturing with a substantially homogeneous population of cells. Moreover, Pereira and Friedman also do not teach or suggest that stromal cell differentiation can be directed much less how such

differentiation would be accomplished in culture. In addition, Caplan has nothing whatsoever to do with differentiation of MSCs and does not teach or suggest that this complex process can be accomplished *in vitro*. Thus, there was not motivation to combine these references to achieve the surprising results disclosed in the present application. Therefore, there would be no motivation to combine these references since the combination does not teach or suggest that stromal cells can be caused to differentiate by co-culturing them with differentiated cells of a desired cell type.

In light of the foregoing arguments, it is clear that there was no reasonable expectation of success in combining the references to devise a method to direct differentiation of stromal cells by co-culturing them with a substantially homogenous population of differentiated cells of the desired cell type. That is, a person of ordinary skill in the art would not expect to succeed in directing differentiation of stromal cells by co-culturing the cells with a population of differentiated cells by combining references (*i.e.*, Pereira, Friedmann and Caplan) that have no suggestion or teaching as to how to direct differentiation of stromal cells *in vitro* using co-culturing them with other cells. As discussed previously elsewhere herein, Pereira, Friedmann and Caplan do not discuss directing stromal cell differentiation at all; instead, these references apparently note that bone marrow-derived cells implanted into a recipient animal can be found in certain tissues and express cell lineage-specific markers in those tissues. Nowhere in these references is there a teaching or suggestion that differentiation can be achieved by co-culturing stromal cells with a population of differentiated cells *in vitro*. Thus, there could be no reasonable expectation of success that combining Pereira, Friedmann and Caplan would result in the present invention.

For the reasons discussed above, the combination of Pereira with Friedmann and Caplan, cannot render claims 19 and 20 *prima facie* obvious under 35 U.S.C. § 103(a) and, therefore, the rejection should be reconsidered and withdrawn.

Summary

Applicants respectfully submit that each rejection of the Examiner to the claims of the present application has been either overcome or is now inapplicable, and that each of claims 1-20, is in condition for allowance. Reconsideration and allowance of each of these claims are respectfully requested at the earliest possible date.

Respectfully submitted,

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(Date)

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RMA/csk

Encs. Schwarz et al. (1999, Hum. Gene Ther. 10:2539-2549)
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